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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,454	02/26/2002	Levav Roiz	02/23357	8094

7590 09/23/2005

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2005

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,454	ROIZ ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14,21-44 and 53-60* is/are pending in the application.

4a) Of the above claim(s) *8-14,21-44 and 53-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment and Dr. Shoseyov's declaration filed 7-5-05 have been entered. Claims 1, 2, 4 and 5 have been amended. Claims 3, 15, 16, 19, 45-52, 61 and 62 have been canceled. Claims 1, 2, 4-14, 21-44 and 53-60 are pending. Claims 1, 2 and 4-7 are under consideration.

The present application was filed containing a power of attorney to Sol Sheinbein and Martin Moynihan. A correspondence address was supplied for Sol Sheinbein. No address was supplied for Martin Moynihan.

Sol Sheinbein was excluded from practice before the Patent and Trademark Office (Office). The Office does not communicate with attorneys or agents who have been suspended or excluded from practice.

As a correspondence address, other than to Sol Sheinbein, is not of record, this Office action is being mailed to the other practitioner of record at his/her last known address as listed on the register of patent attorneys and agents. To ensure that a copy of this Office action is received in a timely manner to allow for a timely reply, a copy of the Office action is being mailed directly to the address of the inventor first named in the declaration or oath. Any reply by applicant(s) should be by way of the remaining practitioner(s) of record and should include a new correspondence address.

Specification

The amendment filed 7-5-05 amending the specification by inserting on page 1 line 4 "This application is a National Phase application of PCT/IL00/00514... **the contents of which are hereby incorporated by reference"** is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The oath/ declaration only claims priorities of PCT/IL00/00514 and 09/385,411 but fails to incorporate herein by reference. Thus, the amendment filed 7-5-05 introduce new matter into the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 2 and 4-7 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventively reducing the number of aberrant crypt foci (ACF) in a rat having **DMH-induced** colon cancer when non-recombinant RNase B1 is administered directly to the colon via osmotic micro-pump, or reducing the number of colon tumor, the tumor size, the number of ACFs or the tumor angiogenesis in a rat having **DMH-induced** colon cancer with oral administration of the non-recombinant RNase B1 microcapsules, and reducing the number and size of tumor, inhibiting the growth of tumor and reducing angiogenesis of tumor in rats treated with osmotic pumps that directly deliver the non-

recombinant RNase B1 to the colon, does not reasonably provide enablement for a method of treating solid tumors in a mammalian subject by using any ribonuclease of the T2 family having an actin binding activity or its mutants that is devoid of ribonuclease activity other than non-recombinant RNase B1 and RNase 6PL via various administration routes, or a method of treating any brain tumor and various tumors other than melanoma and colon cancer as disclosed in a mammalian subject by using RNase B1 and RNase 6PL having an actin binding activity or its mutants that is devoided of ribonuclease activity via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 1-12-05. Applicant's arguments filed 7-5-05 have been fully considered but they are not persuasive.

Claims 1, 2, 4 and 5 have been amended to read on a method of treating a solid tumor in a mammalian subject by administering to the subject a ribonuclease of the T2 family having an actin binding activity or said T2 ribonuclease that is devoid of ribonucleolytic activity.

Applicants cite Table II and Dr Shoseyov's declaration and argue that the T2 RNase having actin binding activity can be used to treat various tumors via various administration routes. Applicants further cite reference Acquati (2005) and human tumor suppressor gene product RNASET2 (identical to RNase 6PL) decreases metastatic potential of a cancer cell line in vivo and the activity was not affected by a double point mutation at the ribonuclease catalytic sites (amendment, p. 14-17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-12-05. The claims read on the use of any ribonuclease of the T2 family proteins having an actin binding activity for treating solid tumors. The claims

encompass known and unidentified ribonucleases of the T2 family proteins. RNases from T2 family are widespread in distribution and encompass ribonucleases isolated from viruses, bacteria, protozoa, fungi, plants, and animals. Although they share some similar structural features it does not necessarily mean that they would all have actin binding activity and ability to inhibit tumor cell growth or ability for treating solid tumors. There are about 50 known T2 family of ribonucleases having molecular weights ranging from 19kDa to 97kDa and they have diverse role in living organisms. They have dramatically different amino acid sequences. Very few information is available on the structure-function correlation except that of RNase Rh and RNase LE. The specification fails to provide the structural features of the ribonuclease of T2 family having actin binding activity and tumor inhibiting activity. The specification only discloses that RNase B1 has actin binding activity and Table I of the amendment filed 7-5-05 shows E. coli RNase I and RNase 6PL have actin binding activity. Table II and Dr. Shoseyov's declaration only discloses reduction of tumor size in vivo by A. niger RNase B1 and RNase 6PL but no in vivo data has been disclosed regarding A. oryzae RNase T2 and E. coli RNase I. It is unclear what contributes to the actin binding in the ribonucleases of T2 family proteins and whether any other ribonuclease of the T2 family proteins has actin binding activity. Different member of the T2 ribonuclease family would have distinct protein sequences and different biological functions. Protein function was unpredictable at the time of the invention from mere amino acid sequence. There is no evidence of record that member of the ribonuclease of T2 family other than RNase B1 and RNase 6PL would bind to actin and inhibit tumor cell growth or reduce tumor size *in vivo*. One skilled in the art at the time of the invention would not know how

to use the ribonuclease of T2 family proteins other than RNase B1 and RNase 6PL to treat solid tumors in a mammalian subject.

In addition, the claims read on the use of a recombinant RNase B1 protein. The specification fails to provide any information regarding the nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein. A search to the prior art also fails to obtain any information regarding the nucleotide sequence encoding the *Aspergillus niger* RNase B1 protein. Therefore, the specification fails to enable the use of a recombinant RNase B1 for the claimed methods.

Further, it was well known in the art that there are many different causes of tumor formation in vivo, for example, genetically speaking, a gene mutation or a combination of different gene mutations, or environmental element, such as UV radiation, X-ray radiation, asbestos, cigarette smoking, and various carcinogens, or a combination of genetic mutation(s) and environmental element(s). The mechanisms of tumor formation from those different causes set forth above could differ from each other dramatically in which numerous factors get in play to form various cancer types and these mechanisms of tumor formation are very likely different from the mechanism of colon cancer formation via injection of DMH of the present invention. Tumors are heterogeneous in their genetic mutations, expression of oncoproteins and response to environmental changes. They need to be considered individually regarding the treatment of cancers in vivo. The data regarding treatment of colon cancer and melanoma with RNase B1 can not be extrapolated into success for treating other tumors and other non-tumor diseases or disorders. There are also various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids, protein

stability, and blood-brain barrier for treating brain tumors. The effectiveness of the RNases B1 and RNase 6PL or their mutants on treating various solid tumors via various administration routes would depend on administration route of the RNase B1 and RNase 6PL, the location of the tumor within the mammalian subject, and the type of tumor targeted.

Applicants argue that solid tumors are commonly defined as any abnormal mass of tissue that usually does not contain cysts or liquid areas and the data in Tables I and II support the enablement of the claimed invention (amendment, p. 18). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-12-05 and the reasons set forth above.

Applicants argue that Table II provides a variety of routes of administration (i.v., i.p. osmotic pump and oral) and direct injection is commonly used in the delivery of drugs to the brain (amendment, p. 19-20). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-12-05 and the reasons set forth above. The claims encompass various administration routes for any type of solid tumor in a mammalian subject. The various types of solid tumor located at numerous different locations in a mammalian subject, therefore, administration route plays an important role in the efficacy of the various ribonuclease of the T2 family administered. Whether a ribonuclease of the T2 family can treat a solid tumor in a mammalian subject depends on the type of ribonuclease used, the administration route, the type of tumor treated, and the location of the target tumor. The specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed. Thus, claims 1, 2 and 4-7 remain rejected under 35 U.S.C. 112, first paragraph.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER